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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,631	02/19/2002	Paul Habermann	DEAV2001/0007USNP	2601

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EXAMINER	
MONDESI, ROBERT B	
ART UNIT	**PAPER NUMBER**
1652	

NOTIFICATION DATE	DELIVERY MODE
06/14/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/076,631	HABERMANN, PAUL	
	Examiner	Art Unit	
	Robert B. Mondesi	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 6-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 6, 2007 has been entered.

Status of the Claims

Claims 2-5 and13-26 have been canceled. **Claims 1 and 6-12** are currently pending and under examination.

Withdrawal of Objections and Rejections

The objections and rejections not explicitly restated below are withdrawn.

Maintenance of rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1 and 6-12 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 6-12 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence prepared as described in Examples 1-3 of the specification and having the signal sequences as set forth at pages 17-18 of the specification, does not reasonably provide enablement for all the possible nucleic acid molecules suggested by the general formula of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use and make the invention commensurate in scope with these claims.

Claim 1 remains provisionally rejected under the judicial created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of US non-provisional application 10/076,634 (1634 Application).

The above rejections were explained in the Office action.

Response to applicants' arguments

In regards to the rejection of claims under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, applicants assert that the Office action does not provide any rationale as to why any particular signal sequence would have been considered to be outside of the generic description provided in the specification and no evidence or argument is advanced in the Office Action as to why the disclosed species should not be considered representative of the genus of claimed molecules.

Applicants' arguments have not been found persuasive. Presently the claims are drawn to a genus of nucleic acid molecules with substantial variation and when there is

substantial variation within the genus and without any functional characteristics. The claims merely recite a structural formula for a product with any particular function and as such lack written description. It is recommended that applicants include language in claims pertaining to the functional characteristic of the genus. Note to applicants, transport peptide is merely a designation for a component of the final product and is not an attempt on the part of applicants to specify the overall functional characteristics of the nucleic acid construct.

In regards to the rejection of the claims under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence prepared as described in Examples 1-3 of the specification and having the signal sequences as set forth at pages 17-18 of the specification, does not reasonably provide enablement for all the possible nucleic acid molecules suggested by the general formula of claim 1, applicants assert that the present invention provides a structure that improves yield of secreted protein.

Applicants assert further that the Office Action speaks to unpredictability relating to a number of nucleic acid molecules. The process of transcription and translation to express a polypeptide or protein is well known in the art. Although there are multiple codons encoding some amino acids, the performance of each codon and its interaction with a corresponding tRNA is well known in the art and thus predictable. Although a large number of nucleic acid molecules can be made, the protein expressed is predictable. Expressing a protein is well known in the art and thus dearly enabled. Therefore merely citing a large number of possible embodiments cannot properly be

relied upon as suggesting a need for undue experimentation. The present genus of molecules recited in claim 1 includes a combination of nucleotides. The combination includes several functional component regions. Each component region is defined in structure and function.

Applicants' arguments have been considered but have not been found persuasive. There is no statement in the claims of the present application that the structure of the construct of the invention improves yield of secreted proteins. Therefore it is noted that the features upon which applicant relies (i.e., improved yield) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The examiner appreciates applicants' understanding of the fact that expressing proteins in isolated host cells using nucleic acids is known in the art; however this has little direct barring on the analysis of the claims with regards to undo burden. The claimed structural formula for the nucleic acid construct of the invention is drawn to an extremely large genus with practically no functional characteristics/limitations. Presently the claimed construct is not required to retain any function. As stated above, applicants' recitation of "transport peptide" is merely to indicate a variable component wherein many different peptides may be used. Presently a person skill in the art would not know how to use the invention commensurate with the scope of the claims. A person skill in the art would most probably be able to make the claimed genus but would not be able to

determine whether each particular species will retain the specific intended function (this being specially worrisome since there are no functional limitations in the claim).

Contrary to applicants' assertions, it is a burden to test all the possible constructs that are represented by the claimed structural formula. A person skill in the art is well aware of the fact that even the slightest change in the sequence of a DNA molecule can lead to a complete loss of function. There is no information in the claims or in the specification that would explain to a person skill in the art as to which portion of the construct is essential for the intended function characteristics- and in a nutshell this is the Patent Offices' understanding of the "structure-function relationship".

To wit, it has long been known how to mutate proteins, but it has been similarly long been known that such mutations are not reasonably predictive of activity for any particular protein. For example, Rudinger (1976) Peptide Hormones, University Park Press, Baltimore, MD., pp. 1-7 discusses the peptide hormones and the characteristics of amino acids as components of the peptide hormones (TITLE). (It is noted that Rudinger discusses peptide hormones, but the general areas of unpredictability are common to all proteins.) In doing so, Rudinger notes that many amino acids may be grouped according to general characteristic (pp. 1-3), and many of these are also classified in two or more classifications (p. 3). Hence, simple mutations of "type" are not reasonably predictable, because there are multiple types to any particular amino acid. Moreover, Rudinger finds that the context of any amino acid is important for structure (pp. 3-4), and that therefore, simple deletions, insertions, or substitutions are also not reasonably predictable, because not only is "type" important, but context is also

important, having longer-range effects than that of simply type. Further, Rudinger discusses the mechanisms of information transfer (e.g, binding and effecting a receptor, which is analogous to any protein binding anything and causing any particular effect) (pp. 4-5). In doing so, Rudinger finds that there exist "patterns" on molecules for recognition, which may involve amino acids close by in the amino-acid polypeptide sequence, or far away (Id.). As such the conformation of the whole molecule is important, and any particular amino acid change, deletion, or addition, may alter the conformation of the molecule enough to affect any particular binding and effect on another molecule.

In analyzing the significance of such observations, Rudinger states that:

In a given molecule, some amino acids or sequences obviously owe their 'significance' to their inclusion in the pattern which is directly involved in recognition by, and binding to, the receptor. However, the fact that the existence of this pattern is dependent on a conformation stabilized by intramolecular interactions, ..., implies that other amino acids or sequences contributing to this conformational stability will be no less 'significant' for the biological activity of the molecule.

(p. 5).

And, in conclusion, Rudinger states:

The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study. The careful design of synthetic analogues, and their

evaluation in biological systems which permit separate analysis of the various phases of hormone action, is the best way to obtaining such information.

(p. 6).

Bowie, et al. (1990) Science, 247 : 1306-10 provides similar insight into the lack of reasonable predictability for the mutation of any particular protein. To wit, Bowie discuses that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). In general, Bowie continues to reflect the observations of Rudinger: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10).

In regards to the provisional rejection of **claim 1** under the judicial created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of US non- provisional application 10/076,634 (1634 Application) applicants have stated that appropriate action will be taken if and when indication of allowable claimed subject matter requires amendment or other action in the conflicting application.

New Rejections and objections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 8 and 11-12 as written, do not sufficiently distinguish over cells that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, he naturally occurring products are considered nonstatutory subject matter.

See American Wood v. Fiber Disintegrating Co., 90 U. S. 566 (1974); American Fruit Growers v. Brogdex Co., 283 U. S. 1 (1931); Funk Brothers Seed Co. v. Kalo Inoculant, 33 U. S. 127 (1948); and Diamond v. Chakrabarty, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or purified". See MPEP 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 6-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Dawson et al. (US Patent 5,434,073; cited in the 5/20/2004 Office action).

The claims are drawn to a nucleic acid sequence as set forth in claim 1, a vector or plasmid comprising said nucleic acid sequence, a host cell comprising said vector or plasmid, and methods for the production of a fusion protein.

Dawson et al. generally teach nucleic acids encoding hirudin fusion proteins. For example, Dawson et al. teach an expression vector encoding a hirudin-hirudin fusion protein comprising a galactose regulated promoter, a nucleotide sequence encoding an alpha-factor pro-peptide with a C-terminal sequence of Ser-Leu-Asp-Lys-Arg, an N-terminal hirudin, a Ile-Glu-Gly-Arg linker, a C-terminal hirudin or a C-terminal streptokinase, and a yeast PGK terminator (See Example 1, columns 11-13 and Examples 8-9, columns 25-27). Dawson et al. teach expression of the hirudin-hirudin or hirudin-streptokinase fusion proteins by culturing Saccharomyces cerevisiae transformed with the expression vector, followed by isolation of the fusion protein (Example 2, columns 13-14 and Example 15, column 32). This anticipates claims 1, 7-14, 21, and 25-28 as written.

Thus Dawson et al. teach all the elements of **claims 1 and 6-12** and these claims are anticipated under 35 USC 102(b).

Conclusion

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B. Mondesi whose telephone number is 571-272-0956. The examiner can normally be reached on 9am-5pm, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert B Mondesi
Examiner
Art Unit 1652

Robert B. Mon
6-5-07